



Medical Genetics Summaries

Providing actionable pharmacogenetic information pertaining to selected medical conditions
<https://www.ncbi.nlm.nih.gov/books/NBK61999/>

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Introduction

Medical Genetics Summaries (MGS) helps the safe and effective prescribing of drugs. Created by NCBI, MGS provides actionable information on the dosing of drugs which are influenced by genetics. Each summary focuses on one drug and includes a description of the drug and its uses, the genes involved in the drug metabolism and efficacy, genetic testing strategies, therapeutic recommendations based on genotype, and nomenclature for the relevant alleles. New summaries are frequently added and every summary undergoes an extensive review process that includes peer review by an international team of clinical and pharmacogenetic experts.

The summaries contain regularly updated pharmacogenetic information from multiple authoritative sources, such as the FDA and professional practice guidelines. Because MGS content contains therapeutic recommendations in a structured format, it is ideally suited for integration in electronic health records (EHR) and hospital systems, and help clinicians who seek evidence-based information to use in clinical settings.

MGS integrates with other NCBI resources including ClinVar, dbSNP, DailyMed, MedGen and the NIH Genetic Testing Registry (GTR) and will continue to evolve to offer healthcare providers up to date medical and genetic testing information.

Access And Term of Use

MGS is freely available from the NCBI Bookshelf (A). The table of contents (partially collapsed) allows easy browsing of the drugs covered so far. The search box (B) enables searching with text terms related to the specific drug or gene of interest. The portlet in the upper right hand corner (insert, C) provides alternative display formats and a PDF download link. The whole book can be downloaded as a PDF, or individual chapters. Excerpts from MGS are also available in related records in GTR and MedGen (D).

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Using MGS Service

An MGS summary can help clinicians to:

- order the most relevant genetic test
- interpret the genetic test results
- find therapeutic recommendations based on genetic test results
- learn about the pharmacogenetics of the drug
- explore related precision medicine resources

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Medical Genetics Summaries

Editors: Victoria Pratt, Howard McLeod, Laura Dean, Adriana Malheiro, Associate Editor, and Wendy Rubinstein, Editor-in-chief.
<https://www.ncbi.nlm.nih.gov/books/NBK61999>

► Editor Information

Bethesda (MD): National Center for Biotechnology Information (US); 2012.

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B Search this book

Medical Genetics Summaries is a growing collection of summaries which describe the impact that specific sequence variations have on health. The summaries review genetic variants that underlie inherited conditions, affect the risk of developing a disease in the future, or influence how an individual may respond to a specific drug.

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Laura Dean.
Created: September 15, 2016.
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E

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Bookshelf ID: NBK61999

GTR, a database of orderable clinical genetic tests
MedGen, a portal to phenotypes with a genetic component

<https://www.ncbi.nlm.nih.gov/gtr>
<https://www.ncbi.nlm.nih.gov/medgen>



MGS Use Cases

We will describe the uses of MGS by presenting a few examples.

Use Case 1: Find information about genetic testing to guide treatment for colorectal cancer

Searching MGS for “colorectal cancer” retrieves summaries for drugs used in colorectal cancer care. One such summary is “Irinotecan Therapy and *UGT1A1* Genotype” (A, with subsection links expanded).

The title links to the entire content of this summary (B). In each summary, the “Go to” portlet on the right (insert, C) outlines its contents. All summaries have the same structured format, beginning with an introduction followed by dosing tables from the FDA and other authoritative guidelines. In this example, the summary is about irinotecan, a drug frequently used to treat metastatic colorectal cancer. Patients carrying certain variants of the *UGT1A1* gene have an increased risk of irinotecan toxicity, which includes severe neutropenia and diarrhea (D). For these patients, the starting dose of irinotecan should be reduced.

Medical Genetics Summaries [Internet].
<https://www.ncbi.nlm.nih.gov/books/NBK294473/>
 Contents ☐ Search this book

Irinotecan Therapy and *UGT1A1* Genotype

Laura Dean, MD.

► Author Information

Created: May 27, 2015; Last Update: April 4, 2018.

Introduction

Irinotecan (brand name Camptosar) is a topoisomerase I inhibitor widely used in the treatment of cancer. It is most frequently used in combination with other drugs to treat advanced or metastatic colorectal cancer. However, irinotecan therapy is associated with a high incidence of toxicity, including severe neutropenia and diarrhea (1).

Irinotecan is converted in the body to an active metabolite known as SN-38, which is then excreted from the body by a UDP-glucuronosyltransferase (UGT) enzyme encoded by the *UGT1A1* gene. Patients with certain variants of the *UGT1A1* gene have a reduced capacity for glucuronidation, a process that transfers glucuronic acid to the drug, making it more water-soluble and easier to excrete from the body.

The “Therapeutic Recommendations” section (F) includes dosing recommendations from the FDA and authoritative guidelines, and provides links to the complete therapeutic recommendations (G).

Display Settings: Summary, Sorted by Relevance Send to:

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Medical Genetics Summaries [Internet].
 Pratt V, McLeod H, Rubinstein W, et al., editors.
 Bethesda (MD): National Center for Biotechnology Information (US); 2012-.

colorectal cancer Search this book

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3. [Capecitabine Therapy and *DPYD* Genotype.](#)
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Introduction
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 Gene: *UGT1A1*
 Genetic Testing
 Therapeutic Recommendations based on Genotype **E**
 Nomenclature of selected *UGT1A1* variants
 Acknowledgments
 Version History
 References
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Go to:

Separate sections of the summary are dedicated to the drug overview, information about the gene(s) that influence the safety and efficacy of the drug, genetic testing, therapeutic recommendations based on genotype, and the nomenclature used for genetic variants (E).

toxicity, including severe neutropenia and diarrhea (1). **D**

Therapeutic Recommendations based on Genotype

Go to:

This section contains excerpted information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2017 Statement from the US Food and Drug Administration (FDA)

Individuals who are homozygous for the *UGT1A1**28 allele (*UGT1A1* 7/7 genotype) are at increased risk for neutropenia following initiation of **Irinotecan** Hydrochloride Injection, USP treatment.

In a study of 66 patients who received single-agent **Irinotecan** Hydrochloride Injection, USP (350 mg/m² once-every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the *UGT1A1**28 allele was 50%, and in patients heterozygous for this allele (*UGT1A1* 6/7 genotype) the incidence was 12.5%. No grade 4 neutropenia was observed in patients homozygous for the wild-type allele (*UGT1A1* 6/6 genotype).

When administered as a single-agent, a reduction in the starting dose by at least one level of **Irinotecan** Hydrochloride Injection, USP should be considered for patients known to be homozygous for the *UGT1A1**28 allele. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment.

UGT1A1 Testing

A laboratory test is available to determine the *UGT1A1* status of patients. Testing can detect the *UGT1A1* 6/6, 6/7 and 7/7 genotypes.

Please review the complete therapeutic recommendations that are located here: (1). **G**

MGS Use Cases (cont.)

Use Case 2: Understand the nomenclature used for genetic variants

In the medical literature, genetic variants are sometimes described in different terms. In the nomenclature section, a table (A) matches the common variant names with the official HGVS expressions. Only the most common and/or significant alleles are listed here, but the table footnote includes a link to a comprehensive listing of all currently known variants (B). The table also links to the relevant records in ClinVar (C), and dbSNP (D), which allow for further investigation of the variants.


Nomenclature of selected *UGT1A1* variants

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
<i>UGT1A1</i> *1	(TA) ₆ TAA	NM_000463.2:c.-53_-52TA[7]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347
<i>UGT1A1</i> *6	211G>A Gly71Arg	NM_000463.2:c.211G>A	NP_000454.1:p.Gly71Arg	rs4148323
<i>UGT1A1</i> *36	(TA) ₅ TAA	NM_000463.2:c.-53_-52TA[6]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347
<i>UGT1A1</i> *28	(TA) ₇ TAA	NM_000463.2:c.-53_-52[8]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347
<i>UGT1A1</i> *37	(TA) ₈ TAA	NM_000463.2:c.-53_-52TA[9]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347

<https://www.ncbi.nlm.nih.gov/books/NBK294473/#irinotecan.Nomenclature>

Use Case 3: Find tests for drug hypersensitivity risk factors in GTR.

The summary for the antiviral drug abacavir (brand name Ziagen) (E) states that *abacavir* is contra-indicated in individuals with a specific variant of the *HLA-B* gene, known as *HLA-B**57:01. This variant increases the risk of hypersensitivity to abacavir, which is a potentially fatal condition. Patients must be screened for *HLA-B**57:01 before starting abacavir therapy. Note: the *HLA-B* gene also impacts on the safety of other drugs. The “Related summaries by Gene” links (F) in the right column link to summaries for 3 such drugs.



Medical Genetics Summaries [Internet].

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<https://www.ncbi.nlm.nih.gov/books/NBK315783/>

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Abacavir Therapy and *HLA-B**57:01 Genotype

Laura Dean, MD.

[Author Information](#)

Created: September 1, 2015; Last Update: April 18, 2018.

Introduction

Abacavir (brand name Ziagen) is used in the treatment of human immunodeficiency virus (HIV) infection. Abacavir is a nucleoside (and nucleotide) reverse transcriptase inhibitor (NRTI), and is used in combination with other medications as part of highly active antiretroviral therapy (HAART) (1).

Hypersensitivity reactions associated include fever, rash, vomiting, and skin peeling. Symptoms typically occur within 10 to 60 days of treatment (11 days median onset) (2).

The presence of *HLA-B**57:01 can be determined in several ways, including sequence analysis of the entire coding region. The “Tests in GTR by Gene” (G) links to tests related to the *HLA-B* gene that were voluntarily deposited in GTR by test providers (laboratories). The Filters allow for selections of relevant tests (H).

Views

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Related Summaries by Gene

- Allopurinol Therapy and *HLA-B**58:01 Genotype
- Carbamazepine Therapy and *HLA* Genotype
- Phenytoin Therapy and *HLA-B**15:02 and *CYP2C9* Genotypes

Related Summaries by Drug Class

- Maraviroc Therapy and *CCR5* Genotype

Tests in GTR by Condition

- Abacavir hypersensitivity

Tests in GTR by Gene

- HLA-B* gene

GTR: GENETIC TESTING REGISTRY

3106[geneid]

Tests (4) Conditions (0) Genes (1) Laboratories (15)

Filters

- Test type**
 - Clinical (4)
- Test purpose**
 - Therapeutic management (4)
- Test method**
 - Deletion/duplication analysis (2)
 - Targeted variant analysis (4)
- Test service**
 - Custom mutation-specific/Carrier testing (2)
- Lab certification**
 - CLIA Certified (2)
 - State Licensed (2)

Results: 1 to 4 of 4

Tests names and labs	Conditions	Genes and analytes	Methods
OneOme RightMed comprehensive test OneOme United States	114	27	<ul style="list-style-type: none"> Deletion/duplication analysis Targeted variant analysis
Abacavir hypersensitivity Genomic Engenharia Molecular Brazil	1	1	Targeted variant analysis
GeneSight Psychotropic Assurex Health, Inc. United States	5	12	<ul style="list-style-type: none"> Deletion/duplication analysis Targeted variant analysis
<i>HLA-B</i>*57:01 genotyping Molecular Genetics, Sunnybrook HSC Sunnybrook Health Sciences Centre Canada	1	1	Targeted variant analysis

MGS Use Cases (cont.)

Use Case 4: Use GTR as a portal to further investigate precision medicine-focused data.

In addition to tests/laboratory information, GTR also lists conditions that are associated with an individual gene. In the same GTR test set discussed in Use Case 3, click the “Genes” button (A) to retrieve the list of conditions.

The individual conditions (B) link to the relevant records for the gene we are interested in (the HLA-B gene). Here, the GTR record for Abacavir hypersensitivity (C) displays an excerpt from MGS and links to the full MGS summary. In the right-hand column, the record also provides links to other relevant resources (D), such as the corresponding record in MedGen (E). The “Professional guidelines” section of the MedGen record lists recent publications on this subject, such as an abacavir dosing guideline (F) with its title linked to the abstract in PubMed (G). The right hand column (H) provides full-text links and links to similar articles for further exploration.

GTR: GENETIC TESTING REGISTRY

3106[geneid] All GTR Search

Tests (21) Conditions (0) **Genes (1)** Laboratories (15)

Results: 1 to 1 of 1 [https://www.ncbi.nlm.nih.gov/gtr/all/genes/?term=3106\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/genes/?term=3106[geneid])

0 selected gene. Check one or more boxes to show tests for any of those genes.

Gene symbol	Associated conditions
<input type="checkbox"/> HLA-B Tests	Abacavir hypersensitivity Allopurinol response Ankylosing spondylitis Carbamazepine hypersensitivity Carbamazepine response Susceptibility to severe cutaneous adverse reaction

Abacavir hypersensitivity

Synonyms: Ziagen hypersensitivity

Summary

Abacavir is a nucleoside reverse transcriptase inhibitor indicated for the treatment of HIV infection, in part of highly active antiretroviral therapy. Although abacavir is generally well tolerated, ~5–8% of patients experience a hypersensitivity reaction (HSR) during the first 6 weeks of treatment. Suspicion of an HSR requires immediate discontinuation because immediate life-threatening reactions can occur. HLA-B is a member of the family and patients with at least one HLA-B*57:01 allele may develop HSR when treated with abacavir. Abacavir pharmacodynamics or pharmacokinetics; it only influences the likelihood that an HSR will occur. Pharmacogenomic tests in dosing for abacavir have been published in Clinical Pharmacology and Therapeutics Implementation Consortium (CPIC) and are available on the PharmGKB website.

Reviews

Medical Genetics Summaries
PubMed Clinical Queries
Reviews in PubMed

Suggested reading

Mallal et al., 2008

Clinical resources

MedGen
PharmGKB
Clinicaltrials.gov

MedGen

Full Report

Abacavir hypersensitivity

MedGen UID: 326759 • Concept ID: C1840547 • Finding

Synonyms: Ziagen hypersensitivity

Drug: Abacavir

Gene (location): HLA-B (6p21.33)

OMIM®: 142830

Definition

Abacavir is a nucleoside reverse transcriptase inhibitor indicated for the treatment of HIV infection, as part of highly active antiretroviral therapy. Although abacavir is generally well tolerated, ~5–8% of patients experience a hypersensitivity reaction (HSR) during the first 6 weeks of treatment. Suspicion of an HSR requires immediate discontinuation because immediate life-threatening reactions can occur. HLA-B is a member of the major histocompatibility complex gene family and patients with at least one HLA-B*57:01 allele may develop HSR when treated with abacavir. HLA-B allele status has no effect on the pharmacokinetics of abacavir. Abacavir pharmacodynamics or pharmacokinetics; it only influences the likelihood that an HSR will occur. Guidelines regarding the use of abacavir have been published in Clinical Pharmacology and Therapeutics Implementation Consortium (CPIC) and are available on the PharmGKB website. [from PharmGKB]

Additional descriptions

Professional guidelines

PubMed

[Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B Genotype and Abacavir Dosing: 2014 update.](#)

Martin MA¹, Hoffman JM², Freimuth RR³, Klein TE⁴, Dong BJ⁵, Pirmohamed M⁶, Hicks JK⁷, Wilkinson MR⁸, Haas DW⁹, Kroetz DL¹; Clinical Pharmacogenetics Implementation Consortium.

Abstract

The Clinical Pharmacogenetics Implementation Consortium (CPIC) Abacavir Dosing were originally published in April 2012. We reviewed the evidence to determine if the therapeutic recommendation in the original publication remains clinically current. However, we have updated and included additional resources for applying CPIC guidelines to the information can be found at PharmGKB (<http://www.pharmgkb.org>).

PMID: 24561393 PMCID: PMC3994233 DOI: 10.1038/clpt.2014.38 [Indexed for MEDLINE] **Free PMC Article**

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Clinical Pharmacogenetics Implementation Consortium gu [Clin Pharmacol Ther. 2013]

Review Abacavir pharmacogenetics—from initial reports to st [Pharmacotherapy. 2013]